REMARKS

Reconsideration is requested.

Claims 1-50 have been canceled, without prejudice.

Claims 51 and 63 have been rewritten in independent form. New claims 70 and 71 are directed to the preferred embodiments wherein the polynucleotide comprises SEQ ID NO: 23. New claim 72 is based on existing claim 51, but specifies that the polynucleotide encodes a polypeptide which binds to antibodies which bind to the polypeptide of SEQ ID NO: 24. New claim 73 refers to a preferred embodiment wherein a vector comprises the polynucleotide of SEQ ID NO: 23. No new matter has been added.

The title of the specification has been amended in response to the Examiner's objection of the previous Title. Withdrawal of the objection of the Title is requested.

The specification has been amended with regard to the term TWEEN®. Withdrawal of the objection to the specification is requested.

The specification was amended as a part of the Preliminary Amendment filed March 22, 2004 to comply with Rule 78. The Examiner is requested to advise the applicants, with specificity, in the event anything further is required in this regard.

The USPTO PAIR IFW contains the formal drawing filed March 22, 2004 as a formal copy of the originally-filed drawing of the parent application. The Examiner's acceptance of the formal drawing is requested.

Return of a completely initialed copy of the previously forwarded PTO 1449 Form, pursuant to MPEP § 609, is again requested as an acknowledgement that the Examiner has considered the art from the parent application.

Rejoinder and allowance of the withdrawn method claims upon allowance of the product claims from which they depend are requested.

To the extent not obviated by the above amendments, the Section 112, first paragraph "written description", rejection of claims 49-65 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following further comments.

Claim 51 is directed to a vector carrying a polynucleotide which encodes the polypeptide of SEQ ID NO: 24 or specific variants thereof. In particular, the only variants which fall within the scope of the claims are those meeting the size and sequence homology requirements of parts (b) and (c) and which also meet the functional requirement that they are able to stimulate an immune response against SEQ ID NO: 24. Claim 51 is thus limited to vectors carrying polynucleotides which encode SEQ ID NO: 24 and variants thereof which have the potential to stimulate an equivalent immune response.

The claims do not require an immune response to be directed against a mycobacterium, but rather the immune response should be directed against the polypeptide of SEQ ID NO: 24. The fragments or variants defined in claim 51 must therefore encode a polypeptide having an equivalent immune response to that of SEQ ID NO: 24. As explained further below, the skilled reader could easily propose a number of variants falling within these definitions which would still encode polypeptides having the ability to stimulate an immune response against SEQ ID NO: 24. For example, using routine methods, the skilled reader could determine the likely sites of immunogenicity within the sequence of SEQ ID NO: 24 and could select fragments or

variants as defined in parts (b) and (c) which retain those immunogenic regions and would therefore be expected to be able to stimulate an immune response against SEQ ID NO: 24.

The Examiner has referred to Greenspan *et al.* as evidence that the structure of an epitope is allegedly difficult to define. However, in order to produce a vector according to part (b) or (c) of claim 51 it is not necessary to carry out a complete structural characterization of the molecular interface between the antigen and antibody as suggested by Greenspan. Rather, it would be sufficient to determine the likely sites of immunogenicity within SEQ ID NO: 24 and to avoid including any mutations in these regions when creating variant sequences, or to ensure that these regions are present in any fragment sequences used.

Attached is a copy of Meister *et al.* (Vaccine 13: 581-591, 1995) which discusses the prediction of epitope locations within protein sequences. This paper was published in April 1995 and thus provides an indication of the state of the art at the priority date.

Meister *et al.* discuss numerous known computer-based algorithms which can predict T cell epitopes from the amino acid sequences of proteins. For example, as suggested in the right hand column of page 581, "*in a previous analysis of the predictive power of the AMPHI algorithm, 70% of published epitopes were shown to contain sequences that would have been predicted by AMPHI*". Meister *et al.* also discuss alternative regions which have been searched for in an attempt to identify peptide epitopes.

Meister *et al.* also describe two particular algorithms, *OptiMer* and *EpiMer,* which were designed to predict T cell epitopes from protein primary structures. These two

algorithms use different criteria based on secondary structural characteristics and/or the density of MHC-binding motifs within the predicted epitopes. Meister *et al.* conclude that "*We have compared these algorithms to previously published methods of epitope identification, and have found that the algorithms are, on the whole, able to predict T cell epitopes from protein primary structure with considerable efficiency and sensitivity per amino acid, in comparison to the overlapping peptide method*" (page 587, column 1, first paragraph).

It can thus be seen that the use of such algorithms to scan amino acid sequences for potential epitope regions was a commonly used procedure at the time this invention was made. Numerous suitable algorithms were available and the ordinarily skilled artisan would have appreciated that, although one could not guarantee to be able to specifically identify every single epitope within a peptide using these algorithms, a good indication of the locations of epitopes within the polypeptide of SEQ ID NO: 24 could have been determined by analyzing its amino acid sequence. As explained above, once the likely locations of such epitopes had been determined, it would be straightforward to ensure that at least one of those regions was included in a polynucleotide according to part (b) or (c) of claim 51. By deleting or substituting only in those regions <u>not</u> identified using such algorithms, the skilled reader could reasonably expect to be able to obtain fragments or variants which meet the functional requirement of being able to stimulate an immune response against the polypeptide of SEQ ID NO: 24.

Withdrawal of the Section 112, first paragraph "written description", rejection I requested.

To the extent not obviated by the above amendments, the Section 112, first paragraph "enablement", rejection of claims 49-65 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following further comments.

As explained above, the claims no longer require the vector to encode a polypeptide which is able to stimulate an immune response against a mycobacterium. Nor do the claims require the polypeptide encoded by the claimed vector to elicit any kind of protective immune response. The claims require that any polypeptide, variant or fragment encoded by the vector is capable of stimulating an immune response which can recognize the polypeptide of SEQ ID NO: 24, for example the variant or fragment is able to bind to the same antibody which binds to SEQ ID NO: 24.

As explained above, despite the specific problems with alanine scanning mutagenesis which Greenspan describes, alternative methods were available at the time of the invention for determining the likely location of epitopes within a polypeptide sequence. For example, algorithms such as those described by Meister *et al.* were in routine use at that time and would have been used by the ordinarily skilled artisan to identify both those regions likely to form part of an epitope, and those regions unlikely to form part of an epitope which could therefore potentially be deleted or mutated. It would not involve undue experimentation to simply take one or more known epitope prediction algorithms and use them to process the amino acid sequence of SEQ ID NO: 24. This would have been routine at the time the invention was made and well within the abilities and knowledge of the skilled reader in this field.

Withdrawal of the Section 112, first paragraph "written description", rejection I requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required in this regard.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
B. J. Sadoff
Reg. No. 36,663

BJS:
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100